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Clinico-epidemiological Characteristics of Kawasaki Disease in COVID-19 Pediatric Patients: A Protocol for Rapid Living Systematic Review

Key Words: Adolescent; Adolescent Health; Child; Child Health; Coronavirus; Coronavirus Infections; COVID-19; Epidemiologic Factors; Signs and Symptoms; Therapeutics

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Abstract

Introduction: The COVID-19 outbreak has posed a major challenge to the healthcare providers. Due to its communicable nature, very stringent public health interventions have been put in place worldwide, yet, it still poses new emerging challenges, one of the most recent being a multisystem inflammatory condition with clinical features resembling Kawasaki-like disease and toxic shock syndrome in children and adolescents. The data on this novel condition is scarce which needs to be reported to identify its clinico-epidemiological and geographical distribution. There is an urgent need to generate evidence for diagnosis and management of this condition in the midst of a pandemic.

Methods and analysis: This systematic review will be conducted using PubMed, Google scholar, ProQuest and EBSCO databases along with grey literature with the aim to identify the clinical features, etio-pathology, laboratory findings, treatment modes and outcomes of Kawasaki-like disease among pediatric patients suffering from COVID-19. Original articles reporting Kawasaki-like disease in COVID-19 pediatric patients will be retrieved after screening by two independent reviewers. Data will be extracted in a specially designed form and studies will be assessed independently for risk of bias. Data will be extracted for the following: author, journal title, publication year, study design, study setting, demographic characteristics (e.g., age, sex, country, ethnicity etc.), sample size, clinical features, etio-pathology, laboratory findings, modes and doses of treatment given, strength and weakness of studies. A descriptive and quantitative analysis will be done for the data.

Ethics and Dissemination: This is a literature based review study with no ethical concerns. We will publish the results in a peer-reviewed journal and present at conference.

Registration Details: CRD42020187427.

Key Words: Adolescent; Adolescent Health; Child; Child Health; Coronavirus; Coronavirus Infections; COVID-19; Epidemiologic Factors; Signs and Symptoms; Therapeutics

Article Summary

Strengths and limitations of this study

- Comprehensive assessment of clinico-epidemiological features of a novel condition will be done in this study.
- This systematic review will inform healthcare providers about this novel condition and ways to manage it.
- During the primary screening phase, reviewers will be blinded to minimize selection bias.
- Data extraction and quality assessment will be performed by independent reviewers, thus minimizing bias and maintaining quality.
- This systematic review is limited to only English language databases and other language databases will not be covered causing language bias.

Introduction

The Coronavirus disease-2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a major challenge to the healthcare providers.(1)(2) Due to communicable nature of this virus, very stringent public health interventions have been put in place worldwide(3,4). Yet, it strives to pose new emerging challenges. The recent being multisystem inflammatory syndrome with clinical manifestations resembling Kawasaki-like disease and toxic shock syndrome in children and adolescents.(5)(6) Although, it has been observed that geriatric people with underlying comorbidities are more vulnerable to severe form

of disease and require intensive care support but a few children getting hospitalized too is evident.(7,8)

Recently, clusters of children and adolescents from Europe and North America were reported to be admitted in intensive care units with a multisystem inflammatory syndrome with clinical features resembling to Kawasaki-like disease and toxic shock syndrome.(9,10) This condition has temporarily been associated with COVID-19 as majority of the cases have shown positive serology in the laboratory investigation.(11)(12) The full range and geographical distribution of the disease is yet not clear owing to the probability of not being recognized in other parts of the world. In order to generate evidence, there should be a standard data collection technique reporting clinical presentation, severity, outcomes, and epidemiology throughout the globe. It is important to understand the causes and risk factors of the condition so that evidence based management can be described.

A preliminary case definition have been given by WHO based on both clinical features as well as laboratory investigations which can be revised in future depending on the availability of more data. The present definition(13) states that any child or adolescent of 0-19 years age, who has fever for 3 or more days along with any two of the five following laid criteria which includes:

1. Muco-cutaneous inflammation which can be oral or on limbs, or rash, or non-purulent conjuctivitis
2. Hypotension or shock
3. Clinical features of cardiac involvement like pericarditis, coronary abnormalities, valvulitis or myocardial dysfunction (including findings of ECHO or higher levels of Troponin/NT-proBNP)
4. Confirmed coagulopathy (evident by PT, PTT, and increased d-Dimers).
5. Having acute gastrointestinal like vomiting, diarrhea or abdominal pain.

This can be accompanied with raised levels of ESR, C-reactive protein, or prolactin marking inflammation. Also, there should not be any other causes of microbial inflammation which includes bacterial sepsis and staphylococcal or streptococcal shock syndromes. All these criteria should also be accompanied by the presence of COVID-19 infection (confirmed by RT-PCR, antigen test or serology positive) or the case be a likely contact of COVID-19 patient.

This case definition will help in identifying and treating the cases at the same time will assist in surveillance too.

In the midst of a pandemic there is an urgent need to collect evidence for diagnosis and management of this new challenge in the form of a syndrome associated with COVID-19 pediatric patients. Hence, in order to generate the most up-to-date evidence, whilst maintaining scientific rigor and quality a systematic review of clinic-epidemiological characteristics of this syndrome is needed. Additionally, studies relevant for these research questions will likely be continuously published in the foreseeable future. Moreover, traditional systematic reviews risk becoming rapidly outdated when new evidence is published almost on a daily basis, and it is not an option to wait till the pandemic is over to publish a systematic review on the full body of evidence. Hence, a rapid systematic review that is continuously updated (living) for this syndrome is necessary. With this background we present the protocol for this systematic review with the following objectives.

Objectives

To present a protocol for rapid living systematic review with the following research questions in mind:

1. What are the clinical and epidemiological features, the etio-pathology, the measures of laboratory findings and their variability, and the treatment modes & doses used among the pediatric patients suffering from COVID-19 along with symptoms of Kawasaki-like disease?
2. What are the outcomes of pediatric patients suffering from COVID-19 and having Kawasaki-like disease?

Methods and Analysis

Standards

This study protocol was developed following Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) reporting guidelines.(14) This systematic review on Clinico-epidemiological Characteristics of Kawasaki Disease in COVID-19 Pediatric Patients will be performed and reported following PRISMA guidelines.

Protocol registration

The protocol for present study is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020187427 registration number).(15) In due course of study, if any change in the protocol will be made it will be updated here.

Eligibility Criteria

Study characteristics/Design

We will include observational studies for this systematic review.

Inclusion

1. Original articles reporting observational studies including case report, case series, cross-sectional, case control, and cohort study, etc.
2. Articles reporting Kawasaki-like disease in children and adolescents suffering from COVID-19.

Exclusion

1. Dissertations, conference proceeding, reviews will be excluded.
2. Studies with no accessible full text versions.
3. Animal studies will not be considered.

Types of participants/population

This study proposes to target COVID-19 pediatric patients exhibiting Kawasaki-like disease.

Inclusion

1. Children and adolescent COVID-19 patients, aged 0-19 years;
2. Living in COVID-19 affected countries;
3. With Kawasaki-like disease symptoms.

Setting and time frame

This systematic review will cover all studies conducted in hospital or clinical settings including special hospitals setup for COVID-19. Articles will be screened from 31st December, 2019 when the initial case of COVID-19 outbreak was reported from China till 5th June, 2020 in order to generate rapid evidence. This review will be living in nature, being updated every two months from first publication till May 2021, at which point the need for further updates, and their regularity, will be reconsidered.

Report Characteristics

English language articles will only be considered for this review. Published articles/ reports along with pre-print versions of the articles will be reviewed. There will be no limitation for date of acceptance or publication.

Information Sources

For this systematic review, electronic databases, websites of international organizations like World Health Organization (WHO), grey literature including reports and researches will form the source of information. A comprehensive search will be done using electronic databases Medline, EBSCO and ProQuest. PubMed and Google Scholar search engines will be used to retrieve studies. PubMed will be used to design search strategy using Medical Subject Headings (MeSH) terms and associated key words. Other frequently used and popular phrases from the existing literature will be used to make the search comprehensive and exhaustive. The same search strategy will be used for other databases also.

Additionally, COVID-19 specific databases (which include preprint repositories) from December 2019 to the current date will also be searched. Preprint repositories to be included are medRxiv (https://www.medrxiv.org/) and bioRxiv (https://www.biorxiv.org/). The EPPI Centre living systematic map of the evidence (http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx) and The COVID-19 Research Database maintained by the World Health Organization (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov) will also be a source of information for this study.

Also, the reference lists of the included articles will be considered as a source of information which will be hand searched.

Search Strategy

The basic search syntax will consist of three concepts Kawasaki disease, COVID-19 and Pediatric population. The MeSH terms used for Kawasaki disease will be “Multisystem inflammatory Syndrome”, “Pediatric multisystem inflammatory disease”, “Hyperinflammatory shock”, “Toxic shock syndrome”, “kawasaki disease”, Vasculitis, **“**pediatric multisystem inflammatory disease, COVID-19 related”; for COVID-19 it will be "COVID-19" [Supplementary Concept] and for pediatric population it will consist of "Child".

All the three concepts will be added using AND i.e. **#1** AND **#2** AND **#3**

The detailed search strategy is available in the supplementary file1.

Study records

Selection Process: In the first phase, titles and abstracts will be screened for potential eligibility by two independent reviewers. During this phase, the reviewers will be blinded to the study details like authors, journal or year of publication to minimize selection bias. The selected articles will further be categorized as relevant, irrelevant and unsure. Any article categorized under irrelevant by both the reviewers will be eliminated. In the second phase, full texts of potentially eligible articles based on the first phase of screening will be obtained. These full text articles will undergo another round of screening based on inclusion and exclusion criteria by two other reviewers. Any dissent over the sieving of the full texts articles will be resolved by the entire team in consensus.

Data Management: A preformed data extraction sheet will be used to extract and enter data by two reviewers independently. These two sheets will be independently assessed by a third reviewer, and compared and checked for disparities. Any potential differences arising, will be discussed and resolved by all three of the former reviewers. If, not resolved, entire team would be contacted to resolve matter in consensus. If any data in the article is found missing, incomplete or unclear, relevant authors will be enquired for the same.

Data items

The following information will be extracted from each article: author, journal title, year of publication, study setting, study design, demographic attributes (like age, sex, country, ethnicity

etc.), sample size, clinical features, etio-pathology, laboratory findings, modes and doses of treatment given, strength and weakness of studies.

Risk of bias in individual studies

Risk of bias will be independently assessed by two reviewers. All studies included for this review will be assessed. We will evaluate risk of bias for observational studies using 'Strengthening the reporting of observational studies in epidemiology' (STROBE) guidelines.(16) A simple pro forma having three domains for assessing selection bias, information bias and confounding will be used. Information bias will include both differential misclassification and non-differential misclassification. Each of the three domains will be marked as either 'Yes' or 'No' for risk of bias. One point for each of the STROBE item will be given and study will be included for review if it has a minimum 12 quality score out of possible 23. Any differences between the two reviewers will be sorted after consulting third reviewer or tie-breaker.

Data synthesis

A descriptive and quantitative synthesis will be used to summarize the results and designs of existing studies. First of all, a range of different clinical & epidemiological features and management done will be presented as narrative synthesis. We will combine the number of cases with individual epidemiological and clinical characteristics, etio-pathology, investigations required and the treatment modes used for each study and calculate the combined percentage of individual clinical symptoms with 95% confidence interval (95% CI). The outcome of each case (e.g., mortality, ICU admissions, complications, etc.) will be reported in the final report in n%. Sub-groups can be formed based on sex, ethnicity etc. which will be analyzed if data permits.

We will try to synthesize the data, even if only two articles are reported.

Ethics and Dissemination

This is a literature based study with no ethical concerns. The data will be obtained from published/ grey literature. Individual patient data is not required hence, eliminating privacy concerns. The results of this study will be published in a peer-reviewed journal and presented at the conference.

Discussion

This systematic review will focus on summarizing the clinical and epidemiological features of a novel challenge faced by the healthcare workers during COVID-19 pandemic. It will generate evidence for assisting in management of disease including laboratory investigations and treatment regimens being used. There is an urgent need to categorize this syndrome but lack of standardized data does not permits this. Our systematic review being rapid and living will help in overcoming this short fall, although robust data collection mechanisms are being developed and advocated worldwide.

This systematic review will follow quality standards as laid in the protocol hence, generating the best possible evidence. The information compiled on the clinical features along with outcomes of the disease will add to the scarce data giving a new direction to the healthcare professionals as well as researchers worldwide.

Strengths and limitations of this study

- Comprehensive assessment of clinico-epidemiological features of a novel condition will be done in this study.
- This systematic review will inform healthcare providers about this novel condition and ways to manage it.
- During the primary screening phase, reviewers will be blinded to minimize selection bias.
- Data extraction and quality assessment will be performed by independent reviewers, thus minimizing bias and maintaining quality.
- This systematic review is limited to only English language databases and other language databases will not be covered causing language bias.

Expected Outcome(s)

1. Epidemiology of disease (incidence/age/sex/ethnicity/comorbidities, etc.).
2. Clinical presentation (e.g., fever, cardiac involvement etc.) and etio-pathology of the disease.
3. Investigations required and modes of treatment used.
4. Clinical outcomes of disease (e.g., mortality, ICU admissions, complications, etc.)

Authors Statement:

AS: Conception of the work, designing the study, drafted the protocol, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

SN: Designing the study, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

PD: Designing the study, Review for intellectual content, final approval of manuscript, Final approval of manuscript, Agreement to be accountable for all aspects of the work

SK: Conception of work, designing the study, drafted protocol, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

SP: Conception of the work, designing the study, Review for intellectual content, Final approval of manuscript, Agreement to be accountable for all aspects of the work

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Author Contributions

All authors (AS, SN, PD, SK and SP) contributed to the development of the search strategy, inclusion/exclusion criteria and data extraction form. Protocol was drafted by AS and reviewed and edited by SN, PD, SK and SP. All authors have approved the final manuscript for submission.

Financial support: None

Conflict of interests: None

Data Statement: All data relevant to the study are included in the article or uploaded as supplementary information.

Supplementary File -1

Detailed search strategy for Medline database/ PubMed

Concept	MeSH Term	Key Words
Kawasaki disease	"Multisystem inflammatory Syndrome"[MESH] "Pediatric multisystem inflammatory disease"[MESH] "Hyperinflammatory shock"[MESH] "Toxic shock syndrome"[MESH] "kawasaki disease"[MESH] Vasculitis[MESH] "pediatric multisystem inflammatory disease, COVID-19 related"[MESH]	"Kawasaki Syndrome"[tiab] "Lymph Node Syndrome, Mucocutaneous"[tiab] "Kawasaki Disease"[tiab] "Mucocutaneous Lymph Node Syndrome"[tiab] "multi-system inflammatory disease, pediatric, COVID-19 related"[tiab] "multi-system inflammatory syndrome, pediatric, COVID-19 related"[tiab] "pediatric multisystem inflammatory syndrome, SARS-CoV-2 related"[tiab] "pediatric multi-system inflammatory disease, COVID-19 related"[tiab] "pediatric multisystem inflammatory syndrome, COVID-19 related"[tiab] "pediatric multi-system inflammatory syndrome, COVID-19 related"[tiab] "pediatric multi-system inflammatory syndrome, SARS-CoV-2 related"[tiab] "multisystem inflammatory disease, pediatric, COVID-19 related"[tiab] "PIMS-TS"[tiab] "pediatric inflammatory multisystem syndrome"[tiab]

		“multisystem inflammatory syndrome in children MIS-C associated with COVID-19”[tiab] “MIS-C associated with COVID-19”[tiab] “MISC associated with COVID-19”[tiab] “multisystem inflammatory syndrome, pediatric, COVID-19 related”[tiab] “Septic Shock”[tiab] “Shock, Toxic”[tiab] “Toxic Shock”[tiab] “Toxic Shock Syndrome”[tiab] “Shock Syndrome, Toxic”[tiab] “Shock Syndromes, Toxic”[tiab] “Syndrome, Toxic Shock”[tiab] “Syndromes, Toxic Shock”[tiab] “Toxic Shock Syndromes”[tiab] “Shock, Endotoxic”[tiab] “Endotoxic Shock”[tiab] “acute febrile mucocutaneous lymph node syndrome”[tiab] KD[tiab] ”lymph node syndrome”[tiab] “Multisystem inflammatory syndrome”[tiab]
COVID-19	"COVID-19" [Supplementary Concept]	“Covid-19”[tiab] “Covid 19”[tiab] “Corona virus disease 19”[tiab]

		"Corona virus disease-19"[tiab] "Coronavirus disease-2019"[tiab] "Coronavirus disease 2019"[tiab] "2019 novel coronavirus disease"[tiab] "COVID19"[tiab] "COVID-19 pandemic"[tiab] "SARS-CoV-2 infection"[tiab] "COVID-19 virus disease"[tiab] "2019 novel coronavirus infection"[tiab] "2019-nCoV infection"[tiab] "coronavirus disease 2019"[tiab] "coronavirus disease-19"[tiab] "2019-nCoV disease"[tiab] "N-Cov Disease"[tiab] "n-Cov disease"[tiab] "COVID-19 virus infection"[tiab] **"Coronavirus** Infection"[tiab] "Infection*, **Coronavirus"[tiab]** "Novel corona virus"[tiab] "Novel corona virus infection*"[tiab] "2019-nCoV"[tiab] "Severe Acute Respiratory Syndrome Coronavirus-2"[tiab] "Severe Acute Respiratory Syndrome Coronavirus-2 disease"[tiab]

Paediatric population	"Child"[Mesh]	Adolescen*[tiab] Teen*[tiab] Teenage*[tiab] Youth*[tiab] “Adolescent*, Female”[tiab] “Female Adolescent*”[tiab] “Adolescent*, Male”[tiab] “Male Adolescent*”[tiab] Preschool[tiab] Child*[tiab] Infant*[tiab]

Search syntax for different concepts after joining MeSH terms and key words with Boolean operator OR

#1 ((((((((((((("Adolescent*"[Mesh]) OR "Child"[Mesh]) OR “Adolescent*, Male”[tiab]) OR "Adolescen*"[tiab]) OR "Teen*"[tiab]) OR "Teenage*"[tiab]) OR "Youth*"[tiab]) OR “Adolescent*, Female”[tiab]) OR “Female Adolescent*”[tiab]) OR “Male Adolescent*”[tiab]) OR Child*[tiab]) OR Preschool[tiab] OR Infant[tiab])))))

#2 ((((((((((((((((((((((((("COVID-19" [Supplementary Concept]) OR “2019 novel coronavirus disease”[tiab]) OR “Covid-19”[tiab]) OR “Covid 19”[tiab]) OR “Corona virus disease 19”[tiab]) OR “Corona virus disease-19”[tiab]) OR “COVID19”[tiab]) OR “Novel corona virus”[tiab]) OR “Novel corona virus infection*”[tiab]) OR “COVID-19 pandemic”[tiab]) OR “SARS-CoV-2 infection”[tiab]) OR “COVID-19 virus disease”[tiab]) OR “2019 novel coronavirus infection”[tiab]) OR “2019-nCoV infection”[tiab]) OR “coronavirus disease 2019”[tiab]) OR “coronavirus disease-19”[tiab]) OR “2019-nCoV disease”[tiab]) OR “COVID-19 virus infection”[tiab]) OR “Coronavirus Infection”[tiab]) OR “Infection*, Coronavirus”[tiab]) OR “Severe Acute Respiratory Syndrome Coronavirus-2 disease”[tiab]) OR “Severe Acute Respiratory Syndrome Coronavirus-2”[tiab]) OR "Coronavirus-2 disease"[tiab]) OR "2019-nCoV"[tiab]) OR "N-CoV Disease"[tiab]) OR "n-CoV disease"[tiab]))

#3 ((((((((((((((((("lymph node syndrome"[tiab]) OR KD[tiab]) OR “MISC associated with COVID-19”[tiab]) OR “multisystem inflammatory syndrome, pediatric, COVID-19 related”[tiab]) OR “Septic Shock”[tiab]) OR “Shock, Toxic”[tiab]) OR “Toxic Shock”[tiab]) OR “Toxic Shock Syndrome”[tiab]) OR “Shock Syndrome, Toxic”[tiab]) OR “Shock Syndromes, Toxic”[tiab]) OR “Syndrome, Toxic Shock”[tiab]) OR “Syndromes, Toxic Shock”[tiab]) OR “Toxic Shock Syndromes”[tiab]) OR “Shock, Endotoxic”[tiab]) OR “Endotoxic Shock”[tiab]) OR “acute febrile mucocutaneous lymph node syndrome”[tiab])) OR ((((((((((((((((((((((Vasculitis[MESH]) OR “pediatric multisystem

inflammatory disease, COVID-19 related"[MESH]) OR "Multisystem inflammatory Syndrome"[MESH]) OR "Pediatric multisystem inflammatory disease"[MESH]) OR "Hyperinflammatory shock"[MESH]) OR "Toxic shock syndrome"[MESH]) OR "kawasaki disease"[MESH]) OR "multisystem inflammatory syndrome in children MIS-C associated with COVID-19"[tiab]) OR "MIS-C associated with COVID-19"[tiab]) OR "Kawasaki Syndrome"[tiab]) OR "Lymph Node Syndrome, Mucocutaneous"[tiab]) OR "Kawasaki Disease"[tiab]) OR "Mucocutaneous Lymph Node Syndrome"[tiab]) OR "multi-system inflammatory disease, pediatric, COVID-19 related"[tiab]) OR "multi-system inflammatory syndrome, pediatric, COVID-19 related"[tiab]) OR "pediatric multisystem inflammatory syndrome, SARS-CoV-2 related"[tiab]) OR "pediatric multi-system inflammatory disease, COVID-19 related"[tiab]) OR "pediatric multisystem inflammatory syndrome, COVID-19 related"[tiab]) OR "pediatric multi-system inflammatory syndrome, COVID-19 related"[tiab]) OR "pediatric multi-system inflammatory syndrome, SARS-CoV-2 related"[tiab]) OR "multisystem inflammatory disease, pediatric, COVID-19 related"[tiab]) OR "PIMS-TS"[tiab]) OR "pediatric inflammatory multisystem syndrome"[tiab] OR "Multisystem inflammatory syndrome"[tiab])))))

Final search syntax after joining all the three concepts with Boolean operator AND

#1 AND #2 AND #3

((((((((((((((((((("lymph node syndrome"[tiab]) OR KD[tiab]) OR "MISC associated with COVID-19"[tiab]) OR "multisystem inflammatory syndrome, pediatric, COVID-19 related"[tiab]) OR "Septic Shock"[tiab]) OR "Shock, Toxic"[tiab]) OR "Toxic Shock"[tiab]) OR "Toxic Shock Syndrome"[tiab]) OR "Shock Syndrome, Toxic"[tiab]) OR "Shock Syndromes, Toxic"[tiab]) OR "Syndrome, Toxic Shock"[tiab]) OR "Syndromes, Toxic Shock"[tiab]) OR "Toxic Shock Syndromes"[tiab]) OR "Shock, Endotoxic"[tiab]) OR "Endotoxic Shock"[tiab]) OR "acute febrile mucocutaneous lymph node syndrome"[tiab])) OR ((((((((((((((((((((Vasculitis[MESH]) OR "pediatric multisystem inflammatory disease, COVID-19 related"[MESH]) OR "Multisystem inflammatory Syndrome"[MESH]) OR "Pediatric multisystem inflammatory disease"[MESH]) OR "Hyperinflammatory shock"[MESH]) OR "Toxic shock syndrome"[MESH]) OR "kawasaki disease"[MESH]) OR "multisystem inflammatory syndrome in children MIS-C associated with COVID-19"[tiab]) OR "MIS-C associated with COVID-19"[tiab]) OR "Kawasaki Syndrome"[tiab]) OR "Lymph Node Syndrome, Mucocutaneous"[tiab]) OR "Kawasaki Disease"[tiab]) OR "Mucocutaneous Lymph Node Syndrome"[tiab]) OR "multi-system inflammatory disease, pediatric, COVID-19 related"[tiab]) OR "multi-system inflammatory syndrome, pediatric, COVID-19 related"[tiab]) OR "pediatric multisystem inflammatory syndrome, SARS-CoV-2 related"[tiab]) OR "pediatric multi-system inflammatory disease, COVID-19 related"[tiab]) OR "pediatric multisystem inflammatory syndrome, COVID-19 related"[tiab]) OR "pediatric multi-system inflammatory syndrome, COVID-19 related"[tiab]) OR "pediatric multi-system inflammatory syndrome, SARS-CoV-2 related"[tiab]) OR "multisystem inflammatory disease, pediatric, COVID-19 related"[tiab]) OR "PIMS-TS"[tiab]) OR "pediatric inflammatory multisystem syndrome"[tiab] OR "Multisystem inflammatory syndrome"[tiab]))))) AND ((((((((((((((((((((((((("COVID-19" [Supplementary Concept]) OR "2019 novel coronavirus disease"[tiab]) OR "Covid-19"[tiab]) OR "Covid 19"[tiab]) OR "Corona virus disease 19"[tiab]) OR "Corona virus disease-19"[tiab]) OR "COVID19"[tiab]) OR "Novel corona virus"[tiab]) OR "Novel corona virus infection*"[tiab]) OR "COVID-19 pandemic"[tiab]) OR "SARS-CoV-2 infection"[tiab]) OR "COVID-19 virus disease"[tiab]) OR "2019 novel coronavirus infection"[tiab]) OR "2019-nCoV infection"[tiab]) OR "coronavirus disease 2019"[tiab]) OR "coronavirus disease-19"[tiab]) OR "2019-nCoV disease"[tiab]) OR "COVID-19 virus infection"[tiab]) OR "Coronavirus Infection"[tiab]) OR "Infection*, Coronavirus"[tiab]) OR

“Severe Acute Respiratory Syndrome Coronavirus-2 disease”[tiab]) OR “Severe Acute Respiratory Syndrome Coronavirus-2”[tiab]) OR "Coronavirus-2 disease"[tiab]) OR "2019-nCoV"[tiab]) OR "N-CoV Disease"[tiab]) OR "n-CoV disease"[tiab])))) AND ((((((((((((("Adolescent*"[Mesh]) OR "Child"[Mesh]) OR “Adolescent*, Male”[tiab]) OR "Adolescen*"[tiab]) OR "Teen*"[tiab]) OR "Teenage*"[tiab]) OR "Youth*"[tiab]) OR “Adolescent*, Female”[tiab]) OR “Female Adolescent*”[tiab]) OR “Male Adolescent*”[tiab]) OR Child*[tiab]) OR Preschool[tiab] OR Infant[tiab])))))

PRISMA-P checklist

Table A.1: PRISMA-P 2015 checklist

Section and topic	Item No.	Checklist Item	Reported on page #
A) Administrative Information			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	Identify protocol as an update of a previous systematic review if applicable	Not Applicable (NA)
Registration	2	Name of registry and registration number	3 + 6
B) Authors			
Contact		Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1 + 2
Contributions		Describe contributions of protocol authors and identify the guarantor of the review	11 +13
Amendments		If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support			
- Sources	5a	Indicate Sources of financial or other support for the review	2 + 13
- Sponsor	5b	Provide name for the review funder and/or sponsor	NA
- Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s) and/or institution(s), if any, in developing the protocol	NA
C) Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3 + 4+ 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
D) Methods			
Eligibility Criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information Sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8 Supplementary file 1
E) Study Records			
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection Process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data Collection Process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data Items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8 + 9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study	9

		level, or both; state how this information will be used in data synthesis	
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8 + 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed	8 + 9

BMJ Open

Clinico-epidemiological Characteristics of Kawasaki-Like Disease in COVID-19 Pediatric Patients: A Protocol for Rapid Living Systematic Review

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Primary Subject Heading:	Public health
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Keywords:	PAEDIATRICS, PUBLIC HEALTH, INFECTIOUS DISEASES, COVID-19, Community child health < PAEDIATRICS

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Clinico-epidemiological Characteristics of Kawasaki-Like Disease in COVID-19 Pediatric Patients: A Protocol for Rapid Living Systematic Review

Key Words: Adolescent; Adolescent Health; Child; Child Health; Coronavirus; Coronavirus Infections; COVID-19; Epidemiologic Factors; Signs and Symptoms; Therapeutics

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Abstract

Introduction: The Coronavirus Disease-2019 (COVID-19) outbreak has posed a major challenge to healthcare providers. Due to its communicable nature, very stringent public health interventions have been put in place worldwide, yet, it still poses new emerging challenges, one of the most recent being a multisystem inflammatory condition with clinical features resembling Kawasaki-like disease and toxic shock syndrome in children and adolescents. The data on this novel condition is scarce which needs to be reported to identify its clinico-epidemiological and geographical distribution. There is an urgent need to generate evidence for diagnosis and management of this condition in the midst of a pandemic.

Methods and analysis: This systematic review will be conducted using Medline database searched through PubMed, Embase, Ovid; and Google scholar, ProQuest and EBSCO databases will also be searched along with grey literature with the aim to identify the clinical features, etio-pathology, laboratory findings, treatment modes and outcomes of Kawasaki-like disease among pediatric patients suffering from COVID-19. Original articles reporting Kawasaki-like disease in COVID-19 pediatric patients will be retrieved after screening by two independent reviewers. Data will be extracted in a specially designed form and studies will be assessed independently for risk of bias. Data will be extracted for the following: author, journal title, publication year, study design, study setting, demographic characteristics, sample size, clinical features, etio-pathology, laboratory findings, modes and doses of treatment given, strength and weakness of studies. A descriptive and quantitative analysis will be completed.

Ethics and Dissemination: This is a literature based review study with no ethical concerns. We will publish the results in a peer-reviewed journal and present at a conference.

Registration Details: CRD42020187427.

Key Words: Adolescent; Adolescent Health; Child; Child Health; Coronavirus; Coronavirus Infections; COVID-19; Epidemiologic Factors; Signs and Symptoms; Therapeutics

Article Summary

Strengths and limitations of this study

- A comprehensive assessment of clinico-epidemiological features of a novel condition will be done in this study.
- This systematic review will inform healthcare providers about this novel condition and ways to manage it.
- During the primary screening phase, reviewers will be blinded to minimize selection bias.
- Data extraction and quality assessment will be performed by independent reviewers, thus minimizing bias and maintaining quality.
- This systematic review is limited to only English language databases and other language databases will not be covered causing language bias.

Introduction

The Coronavirus disease-2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a major challenge to healthcare providers.(1)(2) Due to the communicable nature of this virus, very stringent public health interventions have been put in place worldwide(3,4). Yet, it strives to pose new emerging challenges. One of the recent being multisystem inflammatory syndrome with clinical manifestations resembling Kawasaki-like disease and toxic shock syndrome in children and adolescents.(5)(6) Although, it has been

observed that older adults with underlying comorbidities are vulnerable to a more severe form of the disease which may require intensive care support, some children are also hospitalized.(7,8)

Recently, clusters of children and adolescents from Europe and North America have reportedly been admitted to intensive care units with a multisystem inflammatory syndrome with clinical features resembling to Kawasaki-like disease and toxic shock syndrome.(9,10) This condition has temporarily been associated with COVID-19 as majority of the cases have shown positive serology in the laboratory investigation.(11)(12) The full range and geographical distribution of the disease is yet not clear owing to the probability of not being recognized in other parts of the world. In order to generate evidence, there should be a standard data collection technique reporting clinical presentation, severity, outcomes, and epidemiology throughout the globe. It is important to understand the causes and risk factors of the condition so that evidence based management can be described.

A preliminary case definition have been given by World Health Organization (WHO) based on both clinical features as well as laboratory investigations which can be revised in future depending on the availability of more data. The present definition(13) states that any child or adolescent of 0-19 years age, who has fever for 3 or more days along with any two of the five following laid criteria which includes:

1. Muco-cutaneous inflammation which can be oral or on limbs, or rash, or non-purulent conjuctivitis
2. Hypotension or shock
3. Clinical features of cardiac involvement like pericarditis, coronary abnormalities, valvulitis or myocardial dysfunction (including findings of Echocardiography (ECHO) or higher levels of Troponin/ N-terminal pro b-type natriuretic peptide (NT-proBNP)
4. Confirmed coagulopathy (evident by Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and increased d-Dimers).
5. Having acute gastrointestinal symptoms like vomiting, diarrhea or abdominal pain.

This can be accompanied with raised levels of Erythrocyte Sedimentation Rate (ESR), C-reactive protein, or prolactin marking inflammation. Also, there should not be any other causes of microbial inflammation which includes bacterial sepsis and staphylococcal or streptococcal shock

syndromes. All these criteria should also be accompanied by the presence of COVID-19 infection (confirmed by Reverse Transcription- Polymerase Chain Reaction (RT-PCR), antigen test or serology positive) or the case be a likely contact of COVID-19 patient.

This case definition will help in identifying and treating the cases at the same time will assist in surveillance too.

In the midst of a pandemic there is an urgent need to collect evidence for diagnosis and management of this new challenge in the form of a syndrome associated with COVID-19 pediatric patients. Hence, in order to generate the most up-to-date evidence, whilst maintaining scientific rigor and quality a systematic review of clinic-epidemiological characteristics of this syndrome is needed. Additionally, studies relevant for these research questions will likely be continuously published in the foreseeable future. Moreover, traditional systematic reviews risk becoming rapidly outdated when new evidence is published almost on a daily basis, and it is not an option to wait till the pandemic is over to publish a systematic review on the full body of evidence. Hence, a rapid systematic review that is continuously updated (living) for this syndrome is necessary. With this background we present the protocol for this systematic review with the following objectives.

Objectives

To present a protocol for rapid living systematic review with the following research questions in mind:

1. What are the clinical and epidemiological features, the etio-pathology, the measures of laboratory findings and their variability, and the treatment modes & doses used among the pediatric patients suffering from COVID-19 along with symptoms of Kawasaki-like disease?
2. What are the outcomes of pediatric patients suffering from COVID-19 and having Kawasaki-like disease?

Methods and Analysis

Standards

This study protocol was developed following Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) reporting guidelines.(14) This systematic review on Clinico-epidemiological Characteristics of Kawasaki-like Disease in COVID-19 Pediatric Patients will be performed and reported following PRISMA guidelines.

Protocol registration

The protocol for present study is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020187427 registration number).(15) In due course of study, if any change in the protocol will be made it will be updated here.

Eligibility Criteria

Study characteristics/Design

We will include observational studies for this systematic review.

Inclusion

1. Original articles reporting observational studies including case report, case series, cross-sectional, case control, and cohort study, etc.
2. Articles reporting Kawasaki-like disease in children and adolescents suffering from COVID-19.
3. Kawasaki-like disease symptoms if not explicitly stated by the authors of included studies, will be inferred by the reviewer.

Exclusion

1. Dissertations, conference proceeding, reviews will be excluded.
2. Studies with no accessible full text versions.
3. In vitro and animal studies will not be considered.

Types of participants/population

This study proposes to target COVID-19 pediatric patients exhibiting Kawasaki-like disease.

Inclusion

1. Children and adolescent COVID-19 patients, aged 0-19 years;

2. With Kawasaki-like disease symptoms.
3. Included cases of COVID-19 infection should be confirmed either by RT-PCR or antigen test or serology positive or the case be a likely contact of COVID-19 patient.

Setting and time frame

This systematic review will cover all studies conducted in hospital or clinical settings including special hospitals setup for COVID-19. Articles will be screened from 31st December, 2019 when the initial case of COVID-19 outbreak was reported from China till 30th September, 2020 in order to generate rapid evidence. This review will be living in nature, being updated every two months from first publication till May 2021, at which point the need for further updates, and their regularity, will be reconsidered.

Report Characteristics

Published articles/ reports along with pre-print versions of the articles will be reviewed. There will be no limitation for language and date of acceptance or publication.

Information Sources

For this systematic review, electronic databases, websites of international organizations like World Health Organization (WHO), grey literature including reports and researches will form the source of information. A comprehensive search will be done using electronic databases Medline, EBSCO and ProQuest. PubMed and Google Scholar search engines will be used to retrieve studies. Additionally, Medline will be covered by searching Embase and Ovid databases. PubMed will be used to design search strategy using Medical Subject Headings (MeSH) terms and associated key words. Other frequently used and popular phrases from the existing literature will be used to make the search comprehensive and exhaustive. The same search strategy will be used for other databases also.

Additionally, COVID-19 specific databases (which include preprint repositories) from December 2019 to the current date will also be searched. Preprint repositories to be included are medRxiv (https://www.medrxiv.org/) and bioRxiv (https://www.biorxiv.org/) . The EPPI Centre living systematic map of the evidence

(http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx) and The COVID-19 Research Database maintained by the World Health Organization (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov) will also be a source of information for this study.

Also, the reference lists of the included articles will be considered as a source of information which will be hand searched.

Search Strategy

The basic search syntax will consist of three concepts Kawasaki disease, COVID-19 and Pediatric population. The MeSH terms used for Kawasaki disease will be "Multisystem inflammatory Syndrome", "Pediatric multisystem inflammatory disease", "Hyperinflammatory shock", "Toxic shock syndrome", "kawasaki disease", Vasculitis, **"**pediatric multisystem inflammatory disease, COVID-19 related"; for COVID-19 it will be "COVID-19" [Supplementary Concept] and for pediatric population it will consist of "Child".

All the three concepts will be added using AND i.e. **#1** AND **#2** AND **#3**

The detailed search strategy is available in the supplementary file1.

Study records

Selection Process: In the first phase, titles and abstracts will be screened for potential eligibility by two independent reviewers. During this phase, the reviewers will be blinded to the study details like authors, journal or year of publication to minimize selection bias. The selected articles will further be categorized as relevant, irrelevant and unsure. Any article categorized under irrelevant by both the reviewers will be eliminated. In the second phase, full texts of potentially eligible articles based on the first phase of screening will be obtained. These full text articles will undergo another round of screening based on inclusion and exclusion criteria by two other reviewers. Any dissent over the sieving of the full texts articles will be resolved by the entire team in consensus.

Data Management: A preformed data extraction sheet will be used to extract and enter data by two reviewers independently. These two sheets will be independently assessed by a third reviewer, and compared and checked for disparities. Any potential differences arising, will be discussed and resolved by all three of the former reviewers. If, not resolved, entire team would be contacted to

resolve matter in consensus. If any data in the article is found missing, incomplete or unclear, relevant authors will be enquired for the same through e-mail.

Data items

The following information will be extracted from each article: author, journal title, year of publication, study setting, study design; demographic attributes such as age, sex, country, ethnicity; sample size, clinical features, investigations, modes and doses of treatment given, Supportive care, outcome, strength and limitations of studies. The detailed data extraction form is available in the supplementary file 2.

Expected Outcome(s)

1. Epidemiology of disease
2. Clinical presentation and etio-pathology of the disease.
3. Investigations required and modes of treatment used.
4. Clinical outcomes of disease such as hospitalized, transfer to other facility, discharged alive, death, ICU admissions, left against medical advice.

Risk of bias in individual studies

Risk of bias will be independently assessed by two reviewers. All studies included for this review will be assessed. We will evaluate risk of bias for observational studies using 'Strengthening the reporting of observational studies in epidemiology' (STROBE) guidelines.(16) A simple pro forma having three domains for assessing selection bias, information bias and confounding will be used. Information bias will include both differential misclassification and non-differential misclassification. Each of the three domains will be marked as either 'Yes' or 'No' for risk of bias. One point for each of the STROBE item will be given and study will be included for review if it has a minimum 12 quality score out of possible 23. Any differences between the two reviewers will be sorted after consulting third reviewer or tie-breaker.

Data synthesis

A descriptive and quantitative synthesis will be used to summarize the results and designs of existing studies. First of all, a range of different clinical & epidemiological features and

management done will be presented as narrative synthesis. We will combine the number of cases with individual epidemiological and clinical characteristics, etio-pathology, investigations required and the treatment modes used for each study and calculate the combined percentage of individual clinical symptoms with 95% confidence interval (95% CI). The outcome of each case such as mortality, ICU admissions and complications will be reported in the final report in n%. Sub-groups can be formed based on sex, ethnicity which will be analyzed if data permits.

We will try to synthesize the data, even if only two articles are reported.

Ethics and Dissemination

This is a literature based study with no ethical concerns. The data will be obtained from published/ grey literature. Individual patient data is not required hence, eliminating privacy concerns. The results of this study will be published in a peer-reviewed journal and presented at a conference.

Patient and Public Involvement

Patients were not involved during any of the stages of this protocol as it is a synthesis of available published data.

Discussion

This systematic review will focus on summarizing the clinical and epidemiological features of a novel challenge faced by the healthcare workers during COVID-19 pandemic. It will generate evidence for assisting in management of disease including laboratory investigations and treatment regimens being used. There is an urgent need to categorize this syndrome but lack of standardized data does not permits this. Our systematic review being rapid and living will help in overcoming this short fall, although robust data collection mechanisms are being developed and advocated worldwide.

This systematic review will follow quality standards as laid in the protocol hence, generating the best possible evidence. The information compiled on the clinical features along with outcomes of the disease will add to the scarce data giving a new direction to the healthcare professionals as well as researchers worldwide.

Authors Statement:

AS: Conception of the work, designing the study, drafted the protocol, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

SN: Designing the study, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

PD: Designing the study, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

SK: Conception of work, designing the study, drafted the protocol, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

SP: Conception of the work, designing the study, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

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Author Contributions

All authors (AS, SN, PD, SK and SP) contributed to the development of the search strategy, inclusion/exclusion criteria and data extraction form. Protocol was drafted by AS and reviewed and edited by SN, PD, SK and SP. All authors have approved the final manuscript for submission.

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Data Statement: All data relevant to the study are included in the article or uploaded as supplementary information.

Supplementary File -1

Detailed search strategy for Medline database/ PubMed

Concept	MeSH Term	Key Words
Kawasaki disease	"Multisystem inflammatory Syndrome"[MESH] "Pediatric multisystem inflammatory disease"[MESH] "Hyperinflammatory shock"[MESH] "Toxic shock syndrome"[MESH] "kawasaki disease"[MESH] Vasculitis[MESH] "pediatric multisystem inflammatory disease, COVID-19 related"[MESH]	"Kawasaki Syndrome"[tiab] "Lymph Node Syndrome, Mucocutaneous"[tiab] "Kawasaki Disease"[tiab] "Mucocutaneous Lymph Node Syndrome"[tiab] "multi-system inflammatory disease, pediatric, COVID-19 related"[tiab] "multi-system inflammatory syndrome, pediatric, COVID-19 related"[tiab] "pediatric multisystem inflammatory syndrome, SARS-CoV-2 related"[tiab] "pediatric multi-system inflammatory disease, COVID-19 related"[tiab] "pediatric multisystem inflammatory syndrome, COVID-19 related"[tiab] "pediatric multi-system inflammatory syndrome, COVID-19 related"[tiab] "pediatric multi-system inflammatory syndrome, SARS-CoV-2 related"[tiab] "multisystem inflammatory disease, pediatric, COVID-19 related"[tiab] "PIMS-TS"[tiab] "pediatric inflammatory multisystem syndrome"[tiab]

		"multisystem inflammatory syndrome in children MIS-C associated with COVID-19"[tiab] "MIS-C associated with COVID-19"[tiab] "MISC associated with COVID-19"[tiab] "multisystem inflammatory syndrome, pediatric, COVID-19 related"[tiab] "Septic Shock"[tiab] "Shock, Toxic"[tiab] "Toxic Shock"[tiab] "Toxic Shock Syndrome"[tiab] "Shock Syndrome, Toxic"[tiab] "Shock Syndromes, Toxic"[tiab] "Syndrome, Toxic Shock"[tiab] "Syndromes, Toxic Shock"[tiab] "Toxic Shock Syndromes"[tiab] "Shock, Endotoxic"[tiab] "Endotoxic Shock"[tiab] "acute febrile mucocutaneous lymph node syndrome"[tiab] KD[tiab] "lymph node syndrome"[tiab] "Multisystem inflammatory syndrome"[tiab]
COVID-19	"COVID-19" [Supplementary Concept]	"Covid-19"[tiab] "Covid 19"[tiab] "Corona virus disease 19"[tiab]

		"Corona virus disease-19"[tiab] "Coronavirus disease-2019"[tiab] "Coronavirus disease 2019"[tiab] "2019 novel coronavirus disease"[tiab] "COVID19"[tiab] "COVID-19 pandemic"[tiab] "SARS-CoV-2 infection"[tiab] "COVID-19 virus disease"[tiab] "2019 novel coronavirus infection"[tiab] "2019-nCoV infection"[tiab] "coronavirus disease 2019"[tiab] "coronavirus disease-19"[tiab] "2019-nCoV disease"[tiab] "N-Cov Disease"[tiab] "n-Cov disease"[tiab] "COVID-19 virus infection"[tiab] **"Coronavirus** Infection"[tiab] "Infection*, **Coronavirus"[tiab]** "Novel corona virus"[tiab] "Novel corona virus infection*"[tiab] "2019-nCoV"[tiab] "Severe Acute Respiratory Syndrome Coronavirus-2"[tiab] "Severe Acute Respiratory Syndrome Coronavirus-2 disease"[tiab]

Paediatric population	"Child"[Mesh]	Adolescen*[tiab] Teen*[tiab] Teenage*[tiab] Youth*[tiab] “Adolescent*, Female”[tiab] “Female Adolescent*”[tiab] “Adolescent*, Male”[tiab] “Male Adolescent*”[tiab] Preschool[tiab] Child*[tiab] Infant*[tiab]

Search syntax for different concepts after joining MeSH terms and key words with Boolean operator OR

#1 ((((((((((((("Adolescent*"[Mesh]) OR "Child"[Mesh]) OR “Adolescent*, Male”[tiab]) OR "Adolescen*"[tiab]) OR "Teen*"[tiab]) OR "Teenage*"[tiab]) OR "Youth*"[tiab]) OR “Adolescent*, Female”[tiab]) OR “Female Adolescent*”[tiab]) OR “Male Adolescent*”[tiab]) OR Child*[tiab]) OR Preschool[tiab] OR Infant[tiab])))))

#2 ((((((((((((((((((((((("COVID-19" [Supplementary Concept]) OR “2019 novel coronavirus disease”[tiab]) OR “Covid-19”[tiab]) OR “Covid 19”[tiab]) OR “Corona virus disease 19”[tiab]) OR “Corona virus disease-19”[tiab]) OR “COVID19”[tiab]) OR “Novel corona virus”[tiab]) OR “Novel corona virus infection*”[tiab]) OR “COVID-19 pandemic”[tiab]) OR “SARS-CoV-2 infection”[tiab]) OR “COVID-19 virus disease”[tiab]) OR “2019 novel coronavirus infection”[tiab]) OR “2019-nCoV infection”[tiab]) OR “coronavirus disease 2019”[tiab]) OR “coronavirus disease-19”[tiab]) OR “2019-nCoV disease”[tiab]) OR “COVID-19 virus infection”[tiab]) OR “Coronavirus Infection”[tiab]) OR “Infection*, Coronavirus”[tiab]) OR “Severe Acute Respiratory Syndrome Coronavirus-2 disease”[tiab]) OR “Severe Acute Respiratory Syndrome Coronavirus-2”[tiab]) OR "Coronavirus-2 disease"[tiab]) OR "2019-nCoV"[tiab]) OR "N-CoV Disease"[tiab]) OR "n-CoV disease"[tiab]))

#3 ((((((((((((((((((("lymph node syndrome"[tiab]) OR KD[tiab]) OR “MISC associated with COVID-19”[tiab]) OR “multisystem inflammatory syndrome, pediatric, COVID-19 related”[tiab]) OR “Septic Shock”[tiab]) OR “Shock, Toxic”[tiab]) OR “Toxic Shock”[tiab]) OR “Toxic Shock Syndrome”[tiab]) OR “Shock Syndrome, Toxic”[tiab]) OR “Shock Syndromes, Toxic”[tiab]) OR “Syndrome, Toxic Shock”[tiab]) OR “Syndromes, Toxic Shock”[tiab]) OR “Toxic Shock Syndromes”[tiab]) OR “Shock, Endotoxic”[tiab]) OR “Endotoxic Shock”[tiab]) OR “acute febrile mucocutaneous lymph node syndrome”[tiab])) OR ((((((((((((((((((((Vasculitis[MESH]) OR “pediatric multisystem

inflammatory disease, COVID-19 related"[MESH]) OR "Multisystem inflammatory Syndrome"[MESH]) OR "Pediatric multisystem inflammatory disease"[MESH]) OR "Hyperinflammatory shock"[MESH]) OR "Toxic shock syndrome"[MESH]) OR "kawasaki disease"[MESH]) OR "multisystem inflammatory syndrome in children MIS-C associated with COVID-19"[tiab]) OR "MIS-C associated with COVID-19"[tiab]) OR "Kawasaki Syndrome"[tiab]) OR "Lymph Node Syndrome, Mucocutaneous"[tiab]) OR "Kawasaki Disease"[tiab]) OR "Mucocutaneous Lymph Node Syndrome"[tiab]) OR "multi-system inflammatory disease, pediatric, COVID-19 related"[tiab]) OR "multi-system inflammatory syndrome, pediatric, COVID-19 related"[tiab]) OR "pediatric multisystem inflammatory syndrome, SARS-CoV-2 related"[tiab]) OR "pediatric multi-system inflammatory disease, COVID-19 related"[tiab]) OR "pediatric multisystem inflammatory syndrome, COVID-19 related"[tiab]) OR "pediatric multi-system inflammatory syndrome, COVID-19 related"[tiab]) OR "pediatric multi-system inflammatory syndrome, SARS-CoV-2 related"[tiab]) OR "multisystem inflammatory disease, pediatric, COVID-19 related"[tiab]) OR "PIMS-TS"[tiab]) OR "pediatric inflammatory multisystem syndrome"[tiab] OR "Multisystem inflammatory syndrome"[tiab]))))

Final search syntax after joining all the three concepts with Boolean operator AND

#1 AND #2 AND #3

((((((((((((((((((("lymph node syndrome"[tiab]) OR KD[tiab]) OR "MISC associated with COVID-19"[tiab]) OR "multisystem inflammatory syndrome, pediatric, COVID-19 related"[tiab]) OR "Septic Shock"[tiab]) OR "Shock, Toxic"[tiab]) OR "Toxic Shock"[tiab]) OR "Toxic Shock Syndrome"[tiab]) OR "Shock Syndrome, Toxic"[tiab]) OR "Shock Syndromes, Toxic"[tiab]) OR "Syndrome, Toxic Shock"[tiab]) OR "Syndromes, Toxic Shock"[tiab]) OR "Toxic Shock Syndromes"[tiab]) OR "Shock, Endotoxic"[tiab]) OR "Endotoxic Shock"[tiab]) OR "acute febrile mucocutaneous lymph node syndrome"[tiab])) OR ((((((((((((((((((((Vasculitis[MESH]) OR "pediatric multisystem inflammatory disease, COVID-19 related"[MESH]) OR "Multisystem inflammatory Syndrome"[MESH]) OR "Pediatric multisystem inflammatory disease"[MESH]) OR "Hyperinflammatory shock"[MESH]) OR "Toxic shock syndrome"[MESH]) OR "kawasaki disease"[MESH]) OR "multisystem inflammatory syndrome in children MIS-C associated with COVID-19"[tiab]) OR "MIS-C associated with COVID-19"[tiab]) OR "Kawasaki Syndrome"[tiab]) OR "Lymph Node Syndrome, Mucocutaneous"[tiab]) OR "Kawasaki Disease"[tiab]) OR "Mucocutaneous Lymph Node Syndrome"[tiab]) OR "multi-system inflammatory disease, pediatric, COVID-19 related"[tiab]) OR "multi-system inflammatory syndrome, pediatric, COVID-19 related"[tiab]) OR "pediatric multisystem inflammatory syndrome, SARS-CoV-2 related"[tiab]) OR "pediatric multi-system inflammatory disease, COVID-19 related"[tiab]) OR "pediatric multisystem inflammatory syndrome, COVID-19 related"[tiab]) OR "pediatric multi-system inflammatory syndrome, COVID-19 related"[tiab]) OR "pediatric multi-system inflammatory syndrome, SARS-CoV-2 related"[tiab]) OR "multisystem inflammatory disease, pediatric, COVID-19 related"[tiab]) OR "PIMS-TS"[tiab]) OR "pediatric inflammatory multisystem syndrome"[tiab] OR "Multisystem inflammatory syndrome"[tiab])))))) AND ((((((((((((((((((((((((("COVID-19" [Supplementary Concept]) OR "2019 novel coronavirus disease"[tiab]) OR "Covid-19"[tiab]) OR "Covid 19"[tiab]) OR "Corona virus disease 19"[tiab]) OR "Corona virus disease-19"[tiab]) OR "COVID19"[tiab]) OR "Novel corona virus"[tiab]) OR "Novel corona virus infection*"[tiab]) OR "COVID-19 pandemic"[tiab]) OR "SARS-CoV-2 infection"[tiab]) OR "COVID-19 virus disease"[tiab]) OR "2019 novel coronavirus infection"[tiab]) OR "2019-nCoV infection"[tiab]) OR "coronavirus disease 2019"[tiab]) OR "coronavirus disease-19"[tiab]) OR "2019-nCoV disease"[tiab]) OR "COVID-19 virus infection"[tiab]) OR "Coronavirus Infection"[tiab]) OR "Infection*, Coronavirus"[tiab]) OR

“Severe Acute Respiratory Syndrome Coronavirus-2 disease”[tiab]) OR “Severe Acute Respiratory Syndrome Coronavirus-2”[tiab]) OR "Coronavirus-2 disease"[tiab]) OR "2019-nCoV"[tiab]) OR "N-CoV Disease"[tiab]) OR "n-CoV disease"[tiab])))) AND ((((((((((((((("Adolescent*"[Mesh]) OR "Child"[Mesh]) OR “Adolescent*, Male”[tiab]) OR "Adolescen*"[tiab]) OR "Teen*"[tiab]) OR "Teenage*"[tiab]) OR "Youth*"[tiab]) OR “Adolescent*, Female”[tiab]) OR “Female Adolescent*”[tiab]) OR “Male Adolescent*”[tiab]) OR Child*[tiab]) OR Preschool[tiab] OR Infant[tiab])))))

Author	Journal Title	Publication Year	Type of Study Design	Study Setting	Sample size/ Number of Cases reported	Country	Ethinicity	Age

Sex									
	Fever	Duration of Fever	Rash	Bilateral Non-purulent conjunctivitis	Oral mucosal inflammation signs	Peripheral cutaneous inflammation signs(hands or feet)	Hypotension (age-appropriate)	Tachycardia (age-appropriate)	

C

Prolonged capillary refill time	Pale/mottled skin	Cold hands/feet	Urinary output<2 ml/kg/hr	Chest pain	Tachypnoea (age-appropriate)	Respiratory distress	Abdominal Pain	Diarrhoea	

:linical Features (Signs & Symptoms)

Vomiting	Cough	Sore throat	Runny Nose	Wheezing	Swollen Joints	Joint pain(arthralgia)	Muscle aches	Skin ulcers

Stiff neck	Fatigue/malaise	Seizures	Headache	Hypotonia/floppiness	Paralysis	Hyposmia/anosmia(loss of smell)	Hypogeusia(loss of taste)	Bleeding (Haemorrhage)

Not able to drink	others	Haemoglobin (g/L)	TotalWBC count	Neutrophils	Lymphocytes	Haematocrit	Platelets

APTT/APTR	PT(seconds)	INR	Fibrinogen(g/L)	Procalcitonin (ng/mL)	CRP(mg/L)	ESR (mm/hr)	D-dimer (mg/L)	IL-6 (pg/mL)

Investigations

Ferritin (ng/mL)	Creatinine	(Sodium (mEq/L)	Potassium (mEq/L)	Urea (BUN) (mmol/L)	Glucose (mmol/L)	Pro-BNP (pg/mL)	Troponin (ng/mL)	Creatinine kinase (U/L)

LDH (U/L)	Triglycerides	ALT/SGPT (U/L)	Total Bilirubin	AST/SGOT (U/L)	Albumin (g/dL)	Lactate (mmol/L)	Chest X-Ray Findings	CT Findings

Ecnocardiography (Pericarditis/myocardial dysfunction/valvulitis/coronary abnormalities	Other cardiac imaging (if any)	Bacterial Pathogen testing (Positive/ Negative/ Not done)	If Positive, Specify	SARS-CoV-2 (RT-PCR)	SARS-CoV-2(Rapid antigen test)	SARS-CoV-2 (Rapid antibody test)	SARS-CoV-2 ELISA	SARS-CoV-2 Neutralization Test

Treatment and Dc

SARS-CoV-2 Other Test	Oral/orogastric fluids	Intravenous fluids	Antiviral	Corticosteroid	IV immune globulin	Immunomodulators	Antibiotic

osages

Antifungal agent	Antimalarial agent	Experimental agent	NSAID	Systemic anticoagulation	other	ICU or high dependency unit admission	Oxygen therapy

		Supportive Care						
Non-invasive ventilation	Invasive ventilation	Inotropes/ vasopressors	Extracorporeal (ECMO) support	Plasma Exchange	HFOV	Blood transfusion		Discharged alive

Outcome					Date of Search	Search Details (Restriction by language, yearetc.) Name of database searhed	Other methods of search
Hospitalized	Transfer to other facility	Death	Left against medical advice	Unkown			

Conflict of Interest	Funding	Strength of Study	Limitations of Study	Authors' Conclusions	STROBE Quality Score

PRISMA-P checklist

Table A.1: PRISMA-P 2015 checklist

Section and topic	Item No.	Checklist Item	Reported on page #
A) Administrative Information			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	Identify protocol as an update of a previous systematic review if applicable	Not Applicable (NA)
Registration	2	Name of registry and registration number	3 + 6
B) Authors			
Contact		Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1 + 2
Contributions		Describe contributions of protocol authors and identify the guarantor of the review	11 +13
Amendments		If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support			
- Sources	5a	Indicate Sources of financial or other support for the review	2 + 13
- Sponsor	5b	Provide name for the review funder and/or sponsor	NA
- Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s) and/or institution(s), if any, in developing the protocol	NA
C) Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3 + 4+ 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
D) Methods			
Eligibility Criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information Sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8 Supplementary file 1
E) Study Records			
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection Process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data Collection Process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data Items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8 + 9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study	9

		level, or both; state how this information will be used in data synthesis	
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8 + 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed	8 + 9

Clinico-epidemiological Characteristics of Kawasaki-Like Disease in COVID-19 Pediatric Patients: A Protocol for Rapid Living Systematic Review

Key Words: Adolescent; Adolescent Health; Child; Child Health; Coronavirus; Coronavirus Infections; COVID-19; Epidemiologic Factors; Signs and Symptoms; Therapeutics

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Abstract

Introduction: The Coronavirus Disease-2019 (COVID-19) outbreak has posed a major challenge to healthcare providers. Due to its communicable nature, very stringent public health interventions have been put in place worldwide, yet, it still poses new emerging challenges, one of the most recent being a multisystem inflammatory condition with clinical features resembling Kawasaki-like disease and toxic shock syndrome in children and adolescents. The data on this novel condition is scarce which needs to be reported to identify its clinico-epidemiological and geographical distribution. There is an urgent need to generate evidence for diagnosis and management of this condition in the midst of a pandemic.

Methods and analysis: This systematic review will be conducted using Medline database searched through PubMed, Embase, Ovid; and Google scholar, ProQuest and EBSCO databases will also be searched along with grey literature with the aim to identify the clinical features, etio-pathology, laboratory findings, treatment modes and outcomes of Kawasaki-like disease among pediatric patients suffering from COVID-19. Original articles reporting Kawasaki-like disease in COVID-19 pediatric patients will be retrieved after screening by two independent reviewers. Data will be extracted in a specially designed form and studies will be assessed independently for risk of bias. Data will be extracted for the following: author, journal title, publication year, study design, study setting, demographic characteristics, sample size, clinical features, etio-pathology, laboratory findings, modes and doses of treatment given, strength and weakness of studies. A descriptive and quantitative analysis will be completed.

Ethics and Dissemination: This is a literature based review study with no ethical concerns. We will publish the results in a peer-reviewed journal and present at a conference.

Registration Details: CRD42020187427.

Key Words: Adolescent; Adolescent Health; Child; Child Health; Coronavirus; Coronavirus Infections; COVID-19; Epidemiologic Factors; Signs and Symptoms; Therapeutics

Article Summary

Strengths and limitations of this study

- A comprehensive assessment of clinico-epidemiological features of a novel condition will be done in this study.
- This systematic review will inform healthcare providers about this novel condition and ways to manage it.
- During the primary screening phase, reviewers will be blinded to minimize selection bias.
- Data extraction and quality assessment will be performed by independent reviewers, thus minimizing bias and maintaining quality.
- This systematic review is limited to only English language databases and other language databases will not be covered causing language bias.

Introduction

The Coronavirus disease-2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a major challenge to healthcare providers.(1)(2) Due to the communicable nature of this virus, very stringent public health interventions have been put in place worldwide(3,4). Yet, it strives to pose new emerging challenges. One of the recent being multisystem inflammatory syndrome with clinical manifestations resembling Kawasaki-like disease and toxic shock syndrome in children and adolescents.(5)(6) Although, it has been

observed that older adults with underlying comorbidities are vulnerable to a more severe form of the disease which may require intensive care support, some children are also hospitalized.(7,8)

Recently, clusters of children and adolescents from Europe and North America have reportedly been admitted to intensive care units with a multisystem inflammatory syndrome with clinical features resembling to Kawasaki-like disease and toxic shock syndrome.(9,10) This condition has temporarily been associated with COVID-19 as majority of the cases have shown positive serology in the laboratory investigation.(11)(12) The full range and geographical distribution of the disease is yet not clear owing to the probability of not being recognized in other parts of the world. In order to generate evidence, there should be a standard data collection technique reporting clinical presentation, severity, outcomes, and epidemiology throughout the globe. It is important to understand the causes and risk factors of the condition so that evidence based management can be described.

A preliminary case definition have been given by World Health Organization (WHO) based on both clinical features as well as laboratory investigations which can be revised in future depending on the availability of more data. The present definition(13) states that any child or adolescent of 0-19 years age, who has fever for 3 or more days along with any two of the five following laid criteria which includes:

1. Muco-cutaneous inflammation which can be oral or on limbs, or rash, or non-purulent conjuctivitis
2. Hypotension or shock
3. Clinical features of cardiac involvement like pericarditis, coronary abnormalities, valvulitis or myocardial dysfunction (including findings of Echocardiography (ECHO) or higher levels of Troponin/ N-terminal pro b-type natriuretic peptide (NT-proBNP)
4. Confirmed coagulopathy (evident by Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and increased d-Dimers).
5. Having acute gastrointestinal symptoms like vomiting, diarrhea or abdominal pain.

This can be accompanied with raised levels of Erythrocyte Sedimentation Rate (ESR), C-reactive protein, or prolactin marking inflammation. Also, there should not be any other causes of microbial inflammation which includes bacterial sepsis and staphylococcal or streptococcal shock

syndromes. All these criteria should also be accompanied by the presence of COVID-19 infection (confirmed by Reverse Transcription- Polymerase Chain Reaction (RT-PCR), antigen test or serology positive) or the case be a likely contact of COVID-19 patient.

This case definition will help in identifying and treating the cases at the same time will assist in surveillance too.

In the midst of a pandemic there is an urgent need to collect evidence for diagnosis and management of this new challenge in the form of a syndrome associated with COVID-19 pediatric patients. Hence, in order to generate the most up-to-date evidence, whilst maintaining scientific rigor and quality a systematic review of clinic-epidemiological characteristics of this syndrome is needed. Additionally, studies relevant for these research questions will likely be continuously published in the foreseeable future. Moreover, traditional systematic reviews risk becoming rapidly outdated when new evidence is published almost on a daily basis, and it is not an option to wait till the pandemic is over to publish a systematic review on the full body of evidence. Hence, a rapid systematic review that is continuously updated (living) for this syndrome is necessary. With this background we present the protocol for this systematic review with the following objectives.

Objectives

To present a protocol for rapid living systematic review with the following research questions in mind:

1. What are the clinical and epidemiological features, the etio-pathology, the measures of laboratory findings and their variability, and the treatment modes & doses used among the pediatric patients suffering from COVID-19 along with symptoms of Kawasaki-like disease?
2. What are the outcomes of pediatric patients suffering from COVID-19 and having Kawasaki-like disease?

Methods and Analysis

Standards

This study protocol was developed following Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) reporting guidelines.(14) This systematic review on Clinico-epidemiological Characteristics of Kawasaki-like Disease in COVID-19 Pediatric Patients will be performed and reported following PRISMA guidelines.

Protocol registration

The protocol for present study is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020187427 registration number).(15) In due course of study, if any change in the protocol will be made it will be updated here.

Eligibility Criteria

Study characteristics/Design

We will include observational studies for this systematic review.

Inclusion

1. Original articles reporting observational studies including case report, case series, cross-sectional, case control, and cohort study, etc.
2. Articles reporting Kawasaki-like disease in children and adolescents suffering from COVID-19.
3. Kawasaki-like disease symptoms if not explicitly stated by the authors of included studies, will be inferred by the reviewer.

Exclusion

1. Dissertations, conference proceeding, reviews will be excluded.
2. Studies with no accessible full text versions.
3. In vitro and animal studies will not be considered.

Types of participants/population

This study proposes to target COVID-19 pediatric patients exhibiting Kawasaki-like disease.

Inclusion

1. Children and adolescent COVID-19 patients, aged 0-19 years;

2. With Kawasaki-like disease symptoms.
3. Included cases of COVID-19 infection should be confirmed either by RT-PCR or antigen test or serology positive or the case be a likely contact of COVID-19 patient.

Setting and time frame

This systematic review will cover all studies conducted in hospital or clinical settings including special hospitals setup for COVID-19. Articles will be screened from 31st December, 2019 when the initial case of COVID-19 outbreak was reported from China till 30th September, 2020 in order to generate rapid evidence. This review will be living in nature, being updated every two months from first publication till May 2021, at which point the need for further updates, and their regularity, will be reconsidered.

Report Characteristics

Published articles/ reports along with pre-print versions of the articles will be reviewed. There will be no limitation for language and date of acceptance or publication.

Information Sources

For this systematic review, electronic databases, websites of international organizations like World Health Organization (WHO), grey literature including reports and researches will form the source of information. A comprehensive search will be done using electronic databases Medline, EBSCO and ProQuest. PubMed and Google Scholar search engines will be used to retrieve studies. Additionally, Medline will be covered by searching Embase and Ovid databases. PubMed will be used to design search strategy using Medical Subject Headings (MeSH) terms and associated key words. Other frequently used and popular phrases from the existing literature will be used to make the search comprehensive and exhaustive. The same search strategy will be used for other databases also.

Additionally, COVID-19 specific databases (which include preprint repositories) from December 2019 to the current date will also be searched. Preprint repositories to be included are medRxiv (https://www.medrxiv.org/) and bioRxiv (https://www.biorxiv.org/) . The EPPI Centre living systematic map of the evidence

(http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx) and The COVID-19 Research Database maintained by the World Health Organization (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov) will also be a source of information for this study.

Also, the reference lists of the included articles will be considered as a source of information which will be hand searched.

Search Strategy

The basic search syntax will consist of three concepts Kawasaki disease, COVID-19 and Pediatric population. The MeSH terms used for Kawasaki disease will be "Multisystem inflammatory Syndrome", "Pediatric multisystem inflammatory disease", "Hyperinflammatory shock", "Toxic shock syndrome", "kawasaki disease", Vasculitis, **"**pediatric multisystem inflammatory disease, COVID-19 related"; for COVID-19 it will be "COVID-19" [Supplementary Concept] and for pediatric population it will consist of "Child".

All the three concepts will be added using AND i.e. **#1** AND **#2** AND **#3**

The detailed search strategy is available in the supplementary file1.

Study records

Selection Process: In the first phase, titles and abstracts will be screened for potential eligibility by two independent reviewers. During this phase, the reviewers will be blinded to the study details like authors, journal or year of publication to minimize selection bias. The selected articles will further be categorized as relevant, irrelevant and unsure. Any article categorized under irrelevant by both the reviewers will be eliminated. In the second phase, full texts of potentially eligible articles based on the first phase of screening will be obtained. These full text articles will undergo another round of screening based on inclusion and exclusion criteria by two other reviewers. Any dissent over the sieving of the full texts articles will be resolved by the entire team in consensus.

Data Management: A preformed data extraction sheet will be used to extract and enter data by two reviewers independently. These two sheets will be independently assessed by a third reviewer, and compared and checked for disparities. Any potential differences arising, will be discussed and resolved by all three of the former reviewers. If, not resolved, entire team would be contacted to

resolve matter in consensus. If any data in the article is found missing, incomplete or unclear, relevant authors will be enquired for the same through e-mail.

Data items

The following information will be extracted from each article: author, journal title, year of publication, study setting, study design; demographic attributes such as age, sex, country, ethnicity; sample size, clinical features, investigations, modes and doses of treatment given, Supportive care, outcome, strength and limitations of studies. The detailed data extraction form is available in the supplementary file 2.

Expected Outcome(s)

1. Epidemiology of disease
2. Clinical presentation and etio-pathology of the disease.
3. Investigations required and modes of treatment used.
4. Clinical outcomes of disease such as hospitalized, transfer to other facility, discharged alive, death, ICU admissions, left against medical advice.

Risk of bias in individual studies

Risk of bias will be independently assessed by two reviewers. All studies included for this review will be assessed. We will evaluate risk of bias for observational studies using 'Strengthening the reporting of observational studies in epidemiology' (STROBE) guidelines.(16) A simple pro forma having three domains for assessing selection bias, information bias and confounding will be used. Information bias will include both differential misclassification and non-differential misclassification. Each of the three domains will be marked as either 'Yes' or 'No' for risk of bias. One point for each of the STROBE item will be given and study will be included for review if it has a minimum 12 quality score out of possible 23. Any differences between the two reviewers will be sorted after consulting third reviewer or tie-breaker.

Data synthesis

A descriptive and quantitative synthesis will be used to summarize the results and designs of existing studies. First of all, a range of different clinical & epidemiological features and

management done will be presented as narrative synthesis. We will combine the number of cases with individual epidemiological and clinical characteristics, etio-pathology, investigations required and the treatment modes used for each study and calculate the combined percentage of individual clinical symptoms with 95% confidence interval (95% CI). The outcome of each case such as mortality, ICU admissions and complications will be reported in the final report in n%. Sub-groups can be formed based on sex, ethnicity which will be analyzed if data permits.

We will try to synthesize the data, even if only two articles are reported.

Ethics and Dissemination

This is a literature based study with no ethical concerns. The data will be obtained from published/ grey literature. Individual patient data is not required hence, eliminating privacy concerns. The results of this study will be published in a peer-reviewed journal and presented at a conference.

Patient and Public Involvement

Patients were not involved during any of the stages of this protocol as it is a synthesis of available published data.

Discussion

This systematic review will focus on summarizing the clinical and epidemiological features of a novel challenge faced by the healthcare workers during COVID-19 pandemic. It will generate evidence for assisting in management of disease including laboratory investigations and treatment regimens being used. There is an urgent need to categorize this syndrome but lack of standardized data does not permits this. Our systematic review being rapid and living will help in overcoming this short fall, although robust data collection mechanisms are being developed and advocated worldwide.

This systematic review will follow quality standards as laid in the protocol hence, generating the best possible evidence. The information compiled on the clinical features along with outcomes of the disease will add to the scarce data giving a new direction to the healthcare professionals as well as researchers worldwide.

Authors Statement:

AS: Conception of the work, designing the study, drafted the protocol, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

SN: Designing the study, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

PD: Designing the study, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

SK: Conception of work, designing the study, drafted the protocol, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

SP: Conception of the work, designing the study, Review for intellectual content, final approval of manuscript, Agreement to be accountable for all aspects of the work

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Author Contributions

All authors (AS, SN, PD, SK and SP) contributed to the development of the search strategy, inclusion/exclusion criteria and data extraction form. Protocol was drafted by AS and reviewed and edited by SN, PD, SK and SP. All authors have approved the final manuscript for submission.

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